

copending Application No. 09/464,685. As Applicants indicated previously, upon issuance of a Notice of Allowance, Applicants will file a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) to obviate this double patenting rejection.

The Rejection of the Claims Under 35 U.S.C. §101 Should Be Withdrawn

Claims 2, 9-14, 18-20, 22-30, and 33-37 are rejected for lack of a patentable utility under 35 U.S.C. §101. This rejection is respectfully traversed.

The Examiner states that claims are rejected "for the same reasons of record as set forth in the Office action mailed 25 August 2000." The Examiner notes that "applicants do indeed provide multiple well established and specific utilities for a GPCR" (Office Action mailed February 12, 2001, page 3). Thus, the remaining issue is the Examiner's statement that "applicants have not clearly demonstrated that the cloned nucleic acid and its encoded polypeptide is actually a GPCR." The Examiner concludes that the present invention lacks utility because the claimed invention is not supported by "clear guidance confirming the asserted GPCR activity" (Office Action, mailed February 12, 2001, page 3). Further, in rejecting the present invention for lack of utility, the Examiner asserts, "that a protein's activity can not be based on primary structure alone" (Office Action mailed August 25, 2000, pages 4-5). For the following reasons the rejections should be withdrawn.

The Present Invention is a GPCR

This rejection is inconsistent with current PTO guidelines. The "Utility Examination Guidelines" (66 Fed Reg. 1092) make it clear that sequence identity is sufficient to establish utility, and that working examples or biochemical evidence are not a requirement for the establishment of utility. The "Utility Examination Guidelines" state, "[w]hen a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." In the present case, the Applicant has asserted such a specific, substantial, and credible

utility, and the Office Action has not presented sufficient evidence to rebut this assertion.

The specification discloses that the sequences of the invention share homology with GPCR proteins and are GPCR proteins. The present application discloses sequence similarity to a known GPCR protein and expression data of the sequences of the invention in various tissues (Figure 5). The Examiner has previously noted that "the specification discloses that the cloned GPCR shares a high score with the seven transmembrane domain rhodopsin family" (Office Action mailed August 25, 2000), showing conservation of amino acid sequences between the sequence of the invention and a known GPCR. The Examiner further acknowledges that the Applicants "provide multiple well established and specific utilities for a GPCR" (Office Action mailed February 12, 2001). Nevertheless, the Examiner maintains the rejection based on 35 U.S.C. §101. The Examiner argues that "the claimed invention lacks patentable utility" because "applicants have not clearly demonstrated that the cloned nucleic acid and its encoded polypeptide is actually a GPCR" (Office Action mailed February 12, 2001, page 3). Applicant respectfully disagrees with this analysis.

The Examiner cites Galperin *et al.* (Office Action mailed August 25, 2001) in support of the argument that sequence to function methods of assigning protein function are prone to errors. However, the findings of this reference are directed to proteins that have "no homologs in current databases or when all database hits are to uncharacterized gene products," overlooking the fact that G protein-coupled receptors have a well-established GPCR domain. The specification discloses the combination of the DRY triplet, the seven transmembrane domains, and the extracellular and intracellular domains known to those of skill in the art as indicators of GPCR proteins. In addition, specification includes a computer-generated alignment of the GPCR protein, rhodopsin, with the amino acid sequence set forth in SEQ ID NO:1 (see Figure 2 of the present application). A description of the rhodopsin-like GPCR protein family can be found in Birnbaumer, L. (1990) *Annu. Rev. Pharmacol. Toxicol.* 30:675-705; Casey, *et al.* (1988) *J. Biol. Chem.* 263:2577-2580; Attwood, *et al.* (1993) *Prot. Engng.* 6:167-176; Schertler, G.F. (1999) *Novartis Found. Symp.* 224:54-66; Yeagle, *et al.* (1998) *Biochem. Soc. Trans.* 26:520-531; Sakmar, T.P. (1998) *Prog. Nucleic Acid Res. Mol. Biol.* 59:1-34; Spiegel, A.M. (1996) *Annu. Rev. Biochem.* 58:143-170; Shenker, A. (1995) *Baillieres Clin. Endocrinol. Metabol.*

9:427-451; Muller, G. (2000) *Curr. Med. Chem.* 7:861-888; Bockaert, *et al.* (1999) *EMBO J.* 18:1723-1729; and Iacovelli, *et al.* (1999) *FASEB J.* 13:1-8.

Further, the Examiner states that “the mere presence of said [homologous] domains do not adequately confer or define specific activities to an isolated polypeptide.” The presence of protein domains is an art-recognized tool for determining the functional class of a protein (Alberts, *et al.* (1994) Molecular Biology of the Cell. 3<sup>rd</sup> Ed. Garland Publishing; Gehring, W.J. (1986) *Bioessays* 5:3-4; Hanks *et al.* (1988) *Science* 241:42-52; Shabb *et al.* (1992) *J. Biol. Chem.* 267:5723-5726; Thornton *et al.* (1989) *Trends Biochem. Sci.* 14:300-304; Creighton, E. (1993) Proteins Structures and Molecular Properties, W.H. Freeman & Co.; Muller, G. (2000) *Curr. Med. Chem.* 7:861-888; Branchek *et al.* (2000) *Trends Pharmacol. Sci.* 21:109-117; Larhammar *et al.* (1993) *Drug Des Discov.* 9:179-188; Fergusson *et al.* (1996) *Can. J. Physiol Pharmacol.* 74:1095-1110; Bockaert *et al.* (1999) *EMBO J.* 18:1723-1729).

Thus, Applicants have demonstrated that the polypeptide of the invention is a G protein-coupled receptor. In fact, it is recognized in the present Office Action that GPCR's have “multiple well-established and specific utilities” (page 3). Applicants assert that all the criteria for the establishment of utility have been met, and respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §101 in view of the remarks set forth herein.

The above remarks and other remarks by the Examiner indicate that the Examiner is applying an elevated standard of utility that is inconsistent with the statute, the guidelines, and applicable case law. Applicants contend that the present invention meets the applicable utility standard, as further discussed below.

The present invention is recognized to have utility by those skilled in the art

Those of skill in the art recognize the benefit of inventions such as the present invention. Those of skill in the art appreciate that rapid advances in technology have led to dramatic changes in the way research is conducted in many molecular-biology-related areas. “Molecular biology has had a dramatic influence” on active drug discovery and research projects in the pharmaceutical industry, particularly those involving GPCRs (Jeffrey M. Stadel, Shelagh

Wilson, and Derk J. Bergsma, (1997) "Orphan G protein-coupled receptors: a neglected opportunity for pioneer drug discovery," Trends Pharmacol. Sci. 18:430, 431). The advances in molecular biology have led to what those in the art consider a "paradigm shift" in the way research and drug discovery is conducted. *Id.* In this new paradigm, the starting point in the process is the identification of new members of gene families such as the GPCR superfamily by "computational or bioinformatic methodologies" (Trends Pharmacol. Sci. 18:430). Thus, in the molecular biology field of the present invention, the discovery of an agent that binds the sequence of the invention is the key step, or "first link" of *Cross*. See, *Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir., 1985) (holding that "[w]e perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question").

As those in the art note, "the potential reward of using this ["reverse molecular pharmacological strategy"] approach is that resultant drugs naturally will be pioneer or innovative discoveries, and a significant proportion of these unique drugs may be useful to treat diseases for which existing therapies are lacking or insufficient" (Stadel *et al.* (1997) Trends Pharmacol. Sci. 18:434). Much is known but much remains to be learned about the mechanisms and domains of previously discovered GPCRs; nevertheless, members of this gene family have been shown to bind a variety of ligands and have been successfully used for drug discovery. See, for example, Stadel *et al.* (1997) Trends Pharmacol. Sci. 18:430. "Because of the proven link of GPCRs to a wide variety of diseases and the historical success of drugs that target GPCRs, we believe that these orphan receptors are among the best targets of the genomic era to advance into the drug discovery process" (Trends Pharmacol. Sci. 18:436). "The fact that GPCRs mediate a broad spectrum of cellular events make these proteins an ideal target for drug interaction and therapeutics" (Norman H. Lee and Anthony R. Kerlavage (1993) *Molecular Biology of G-Protein-Coupled Receptors*, 6 DN&P 488). This differs from Examiner's argument that the multiplicity of cellular roles associated with GPCRs detracts from the utility of the GPCR of the invention (Office Action mailed February 12, 2001, page 3).

The economic benefits that can result from these advances in the field are well known.

One example is the events of 1994-1997 leading to Merck's marketing of the painkiller Vioxx, described in Gardiner Harris, *The Cure: With Big Drugs Dying, Merck Didn't Merge—It Found New Ones*, The Wall Street Journal, January 10, 2001, at A1. Merck's search for a novel pharmacologically suitable painkiller made use of *in vitro* screens to find drugs that inhibited the activity of Cox-2 but not Cox-1. Such drugs would inhibit prostaglandin production in most of the body but not the gut, thereby ameliorating pain while avoiding undesirable side effects. Candidate drugs from a collection of hundreds of synthesized drugs were first subjected to *in vitro* screening; a much smaller number of successful *in vitro* candidates advanced to *in vivo* screening in mice, and two successful nontoxic drugs from the mouse *in vivo* screens were advanced to even more expensive human clinical trials. Only one of these two drugs showed efficacy in clinical trials, ultimately received FDA approval, and is now being marketed as Vioxx. This example illustrates how a "real world" benefit can be obtained from distinguishing gene family members. This example also illustrates the uncertainty in the field of pharmacology. Despite this uncertainty, as discussed above, the utility of pharmacologically active compounds has been consistently upheld, "*even though it may eventually appear that the compound is without value in the treatment of humans.*" *In re Krimmel*, 292 F.2d 948 (C.C.P.A. 1961); see also *Cross*, 753 F.2d at 1050 (finding the utility standard fulfilled for a claimed compound where "based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity"). Applicants contend that the present invention is at least as useful as the pharmacological compounds of *In re Krimmel*, *Nelson*, and *Cross*, and thus that the present invention satisfies the standard of utility under 35 U.S.C. §101.

The Examiner's rejection of the current invention for lack of utility is at odds with the PTO guidelines and supporting case law:

The PTO guidelines state that "[a]n applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." 66 Fed. Reg. 1098. This regulation is consistent with *Cross*, which held that "[w]hen a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown."

*Cross*, 753 F.2d at 1046 ln9, citing *Raytheon Co. v. Roper Corp.* 724 F.2d 951, 958 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984). Thus, the Examiner's utility rejection depends on the invalidity of each of Applicants' asserted uses.

The PTO guidelines state that "[a] rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record." 66 Fed. Reg. 1098. Further, the guidelines state that "[c]redibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record...that is probative of the applicant's assertions." 66 Fed. Reg. 1098. Applicants have provided support for the assertion that one of ordinary skill in the art would find the present invention useful for a variety of uses and thus the utility standard is met.

The PTO guidelines state:

"[w]here the asserted utility is not specific or substantial, a *prima facie* showing [of no specific and substantial credible utility] must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements: (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed is not both specific and substantial nor well-established; (2) Support for factual findings relied upon in reaching this conclusion; and (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art."

66 Fed. Reg. 1098. Further, "Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." 66 Fed. Reg. 1098-99.

This provision is consistent with the case law. See, *In re Gazave*, 379 F.2d 973

(C.C.P.A. 1967) (finding that the utility standard was met where “appellant’s assertions of usefulness in his specification appear to be believable on their face and straightforward, at least in the absence of reason or authority in variance”); *Ex parte Dash*, 27 U.S.P.Q.2d 1481, 1484 (Bd. Pat. App. & Int’f 1993) (holding that “[a] disclosure of a utility satisfies the utility requirement of section 101 unless there are reasons for the artisan to question the truth of such disclosure”). Similarly, in *In re Jolles*, claims to pharmaceutical compounds and methods of use were rejected under §101 and §112. The court held, “it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct.” 628 F.2d 1322, 1327 (C.C.P.A. 1980). See also, *In re Brana*, 51 F.3d 1560, 1563 (Fed. Cir.1995) (stating that “[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention’s asserted utility,” and holding that the PTO did not meet this burden).

Applicants contend that in the present case, the Examiner has not supported the utility rejection in the required manner. Rather, the Examiner has primarily restated Applicants’ arguments and then made bare assertions that the utility requirement is not met. The Examiner has not made a *prima facie* showing of no utility, and the rejection should be withdrawn.

The Examiner’s rejection results from an incorrect application of PTO guidelines:

As a further indication that the Examiner is applying the incorrect utility standard, the Examiner’s analysis is inconsistent with PTO guidelines. The “Utility Examination Guidelines” (66 Fed Reg. 1092) make it clear that sequence identity is sufficient to establish utility, and that working examples or biochemical evidence are not a requirement for the establishment of utility. The “Utility Examination Guidelines” state that, “[w]hen a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion.” In the present case, Applicants have asserted such a specific, substantial, and

credible utility, and the Office Action has not presented sufficient evidence to rebut this assertion. The Examiner's analysis seems to require that for agents or compositions, including antibodies, that detect, bind, or modulate a polypeptide to have utility, the polypeptide must be purified and biochemically characterized with regards to ligands, activated molecules, and the resulting signal transduction cascade. However, the requirement the Examiner wishes to impose is far beyond the utility standard required of other inventions in this and related fields. The Examiner has presented no evidence or reasoning to refute that those of ordinary skill in the art are aware that agents or compositions, including antibodies, that detect, bind, or modulate a polypeptide such as those of the present invention have utility, as Applicants have asserted throughout the specification and as detailed herein. Therefore, the Examiner has not overcome the presumption that the present invention has the requisite utility.

The Office Action restates most of Applicants' arguments in the response filed November 11, 2000, but then dismisses these arguments without explanation in a conclusory manner that does not satisfy the requirements of examination. For example, in maintaining the rejection of the present claims, the Examiner notes Applicants' arguments concerning the homology between the sequences of the present application and known GPCR proteins, but does not address this argument (Office Action mailed February 12, 2001, pages 3-4). Instead, the Examiner dismisses Applicants' analysis of the amino acid sequence of the invention by noting that "the mere presence of said domains" is insufficient for characterization of the polypeptide. This analysis misses the point of the Revised Utility Guidelines, which do not require that a polypeptide's precise physiological role be known as a requirement of patentability. Further, the Examiner cites no support for the proposition that a polypeptide's precise physiological role be known as a requirement for patentability.

In view of the foregoing remarks, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §101 should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should be Withdrawn

Claims 2, 9-14, 18-20, 22-30, and 33-37 are rejected under 35 U.S.C. §112, first



paragraph. This rejection is respectfully traversed.

The Examiner asserts (in the Office Action mailed February 12, 2001) that “[s]ince the claimed invention is not supported by a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.” Applicants respectfully disagree with this assessment. Applicants have provided many particular citations in the application which support Applicants’ assertions of utility and operability; further, those of skill in the art are familiar with routine techniques that enable those of skill to use the present invention in the asserted utilities. See, for example, Stadel, *et al.* (1997) , “Orphan G protein-coupled receptors: a neglected opportunity for pioneer drug discovery,” *Trends Pharmacol. Sci.* 18:430, 431; C. Wagener, (1997) “Molecular diagnostics,” *J. Mol. Med.* 75:728; U. Landegren and M. Nilsson (1997) “Locked on target: strategies for future gene diagnostics,” *Ann. Med.* 29:585; M.G. Rusnak, (1995) “Biotechnology of diagnostics: emerging opportunities,” *Biotechnology* 13:1056. Applicants note that “where those of ordinary skill in the art will know how to use, the applicant has a right to rely on such knowledge” *In re Nelson*, 280 F.2d 172, 184 (C.C.P.A. 1960).

Applicants believe that the Office Action has mistakenly confounded the §101 standard with the §112 standard, to the detriment of Applicant. It is true that “[t]he lack of utility because of inoperativeness (a question of fact), and the absence of enablement (a question of law) are closely related grounds of unpatentability.” *Ex parte Dash*, 27 U.S.P.Q.2d 1481, 1484 (Bd. Pat. App. & Int’f 1993). However, the Examiner indicates that the rejection of claims 2, 9-14, 18-20, 22-30, and 33-37 under 35 U.S.C. §112 were also maintained, because “since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.” (Office Action mailed February 12, 2001, page 4). Thus, here, as in *In re Nelson*, 280 F.2d 172 (C.C.P.A. 1960), overruled in part by *In re Kirk*, 376 F.2d 936 (C.C.P.A. 1967), the Examiner has incorrectly “taken the position that appellants have not complied with §112, but it has not shown why this is so except by objection to the kind of utility disclosed, which presents an issue under §101 rather than §112.” 280 F.2d at 177. Further,

“what the Patent Office is really trying to insist on here has nothing to do with the ‘how to use’ provision of §112. It is demanding some different, or greater, or more commercial or more mundane use than the one disclosed.” *Id.* at 183. Finally, the *Nelson* court said: “[m]uch confused thinking on this matter has resulted from a failure to separate the requirement of §101 that an invention be useful from the §112 requirement that the specification shall so explain ‘the manner and processes of ... using’ the invention as to ‘enable any person skilled in the art ... to ... use the same.’” *Id.* at 184.

Applicants urge that this distinction should be carefully maintained in reviewing the present case, because the confusion of issues here has made it difficult to fully understand the basis of the present rejection. Applicants dispute the Office Action’s contention that, with regard to the “how to use” requirement, Example 10 of the training materials requires Applicants to identify the specific cellular activity of the GPCR to which the claimed agents and compositions detect, bind, or modulate are directed (Office Action mailed February 12, 2001, pages 3-4). To rebut the Examiner’s argument, Applicants cite *Cross* to support the proposition that “an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor’s theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. §112.” *Cross*, 753 F.2d at 1042, citing *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983); see also, *In re Chilowsky*, 229 F.2d 457, 463 (C.C.P.A. 1956) (holding that “if the disclosure is sufficient to enable the ordinary skilled worker in the art to practice the invention, it is immaterial whether the applicant understood or explained all the principles underlying it”). Applicants believe that, as discussed above, the “how to use” requirement has been met in the present application.

Applicants note that claims are presumed to be enabled under §112: “a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of

the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971). “Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.” *Id.* at 223. Applicants contend that here, there is not reason to doubt Applicants’ assertions concerning enablement; one of skill in the art would be able to make and use the claimed invention with only the exercise of routine practices, as discussed above. The Examiner has not advanced sufficient grounds for questioning the accuracy of Applicants’ statements, and the rejection under §112 should be withdrawn.

Further, the courts recognize that the public benefit is served by early disclosure of inventions. In *In re Bundy*, 642 F.2d 430, 432-33 (C.C.P.A. 1981), applicant’s claims were directed to compositions of prostaglandins. The court held that applicant complied with §112 where applicant disclosed that the claimed compounds were useful and used in the same manner as known related compounds, noting that “[e]arly filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public.” *Id.* at 433. Applicant notes that varying standards of enablement should not be applied to different fields of invention. In *In re Chilowsky*, 229 F.2d 457, 463 (C.C.P.A. 1956), the court held that while “[t]he character and amount of evidence needed may vary, ... the degree of certainty as to the ultimate fact of operativeness or inoperativeness should be the same in all cases.” *Id.* at 462.

Thus, for all of these reasons, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

### CONCLUSIONS

In view of the above arguments, Applicants respectfully submit that all grounds of rejection under 35 U.S.C. §101 and §112 have been overcome. Reconsideration and withdrawal

of the rejections are therefore respectfully requested.

The Examiner is respectfully requested to withdraw the rejections and allow Claims 2, 9-14, 18-20, 22-30, and 33-37. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of further prosecution. The amendments were not made earlier because applicant earnestly believes that the specification is enabling for the breadth of the claims as originally drafted, or the amendments were made pursuant to suggestions made by the Examiner.

Applicants believe that the present application is now in a condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. The Applicants note that upon an indication of allowability, the Applicants may choose to rewrite claims with Markush groups into separate and independent claims.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

In re: Glucksmann, et al.

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Respectfully submitted,



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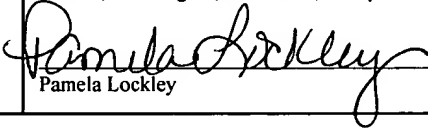
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